

**ORAL COMPOSITIONS OF FENRETINIDE HAVING INCREASED
BIOAVAILABILITY AND METHODS OF USING THE SAME**

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Related Applications

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The present application claims the benefit of provisional application Serial No. 60/444,530, filed January 31, 2003, the disclosure of which is incorporated by reference herein in its entirety.

Field of the Invention

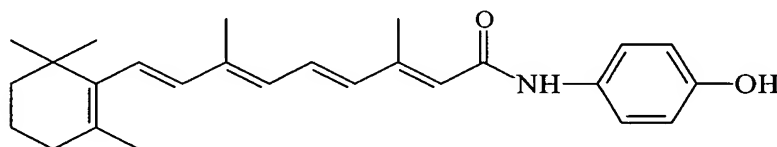
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The present invention concerns pharmaceutical compositions for oral delivery of a retinide such as fenretinide.

Background of the Invention

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Fenretinide [HPR; all-*trans*-N-(4-hydroxyphenyl)retinamide; CAS Registry number 65646-68-6] is a synthetic retinoic acid derivative having the structure:



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Fenretinide is minimally soluble in aqueous solution. U.S. Patent No. 4,665,098 by Gibbs describes an oral pharmaceutical composition of fenretinide as useful for the treatment of breast and bladder cancer. However, the bioavailability of this oral fenretinide composition is limited and greater anticancer effects might be obtained if fenretinide could be delivered intravenously to achieve higher drug plasma levels. Hence, there currently remains a need for new pharmacological compositions of fenretinide, especially for oral administration which provide for both satisfactory

solubility, and plasma and tissue bioavailability, especially in patient populations generally less tolerant of capsule, tablet, or other non-chewable or non-imbibible drug delivery vectors.

Intravenous formulations of 4-HPR have recently been developed that obtain
5 significantly higher 4-HPR plasma (30 - 120 μ M) and tissue levels in rodent and
canine animal models than the current oral capsule formulation while retaining
minimal systemic toxicity (results not shown). However, this formulation is intended
for use in the inpatient setting in conjunction with intravenous safinol (used as a
ceramide metabolism modulator). Thus, there remains a need for an improved oral
10 formulation of 4-HPR for outpatient use, such as in maintenance therapy during states
of minimal residual disease, or in the palliative care setting, that is easier to administer
and that has improved bioavailability. Such a formulation would be particularly
advantageous for small children and elderly adults in which compliance with the
schedules of the current oral capsular 4-HPR is problematical. Further, an improved
15 oral formulation would facilitate the combination of 4-HPR with ceramide modulating
agents in the outpatient setting.

Formulations of fenretinide suitable for high dose parenteral delivery are
described in PCT Application WO 02/05869 to Gupta et al.

Formulations of fenretinide suitable for oral delivery are described in US
20 Patent No. 5,972,911 and US Patent No. 4,874,795.

Summary of the Invention

The present invention provides an edible composition for oral delivery of an
active agent such as a retinide. The composition comprises or consists essentially of,
25 in the form of a dry flowable powder:

(a) an active agent such as a retinide, preferably in an amount by weight of
from 1 to 10 percent;

(b) lipid matrix composition, preferably in an amount by weight of from 5 to
40 percent (the composition preferably being one comprising or consisting essentially
30 of at least one fatty acid, at least one monoglyceride, and lysophosphatidylcholine,
and the lipid matrix composition preferably containing not more than 7 or 8 moles
water per mole of lipid matrix);

(c) optionally sweetener, which when present may be included in an amount by of from 1 to 30 percent;

(d) flour, preferably in an amount of from 20 to 80 percent by weight; and

(e) optionally humectant, in an amount by weight of from 0 or 1 to 16 percent.

5 In one preferred embodiment, the lipid matrix composition may comprise (i) at least one non-esterified fatty acid (*e.g.*, one having 14 to 22 carbon atoms), (ii) at least one monoglyceride which is a monoester of glycerol and a fatty acid (*e.g.*, the fatty acid having 14 to 22 carbon atoms), and (iii) lysophosphatidylcholine(*e.g.*, one in which in which the fatty acid moiety has 14 to 22 carbon atoms). The fatty acids and
10 monoglycerides may together comprise from 60 or 70 mole percent to 99 mole percent of the lipid matrix composition. The molar ratio of the fatty acids to the monoglycerides may be from 4:1 or 2:1 to 1:2 or 1:4. The lysophosphatidylcholine may comprise from 1 mole percent to 30 or 40 mole percent of the lipid matrix composition.

15 As discussed in greater detail below, compositions of the invention may be packaged in bulk or unit dosage form. Compositions of the invention may be administered *per se* or mixed with a solid or liquid food carrier, for direct oral consumption by a subject or administration through a feeding tube.

Thus, a further aspect of the present invention is a method of treating a
20 disorder such as a proliferative disease in a subject in need thereof, comprising feeding or administering the subject a composition as described above in an amount effective to treat that disorder (such as a proliferative disease).

A still further aspect of the present invention is the use of an active agent as described herein for the preparation of a composition as described herein.

25 PCT Application WO 03/031593 describes acidified, protonated aqueous, predominantly inverse hexagonal phase LYM-X-SORB™ compositions containing proteins, sugars and starches as a nutritional supplement, but does not suggest the use or formulation of non-acidic, minimally hydrated, predominantly lamellar phase LYM-X-SORB™ compositions containing proteins, sugars and/or starches for
30 administering active agents such as fenretinide.

The foregoing and other objects and aspects of the present invention are explained in greater detail in the drawings herein and the specification set forth above.

Brief Description of Drawings

Figure 1. Comparison of 4-HPR in LXS matrix vs Capsule Formulation at 120 mg/kg/day. Cohorts of five mice were feed with 120 mg/kg/day of 4-HPR formulated in various LXS compositions, or 4-HPR expressed from capsules, mixed with mouse chow or Slim-Fast®, divided BID, x 4.5 days. Animals were sacrificed 3 hrs after the last dose and 4-HPR levels in plasma and tissues were assayed by HPLC. Results showed that certain LXS formulations obtained higher levels than the 4-HPR capsule formulation. PLASMA: G1 vs capsule, $P=0.006$; LYM-X 5.59 vs capsule, $P=.06$; LIVER: G1 vs capsule, $P=.013$; LYM-X 5.59 vs capsule, $P=0.045$; LUNGS: G1 vs capsule, $P=0.028$; G2 vs capsule, $P=0.05$; KIDNEY: G1 vs capsule, $P=0.007$; LYM-X 5.59 vs capsule, $P=0.06$; BRAIN: G1 vs capsule, $P=0.01$; LYM-X 5.58 vs capsule, $P=0.02$. Statistical analysis by Student's t -test. Columns, in each set of columns, in sequence from left to right, represent LYM-X 5.57, LYM-X 5.58, LYM-X 5.60, LYM-X 5.59, Capsule Lot #R-6124, LYM-X 5.60 GI (SLIMFAST™), and LYM-X 5.60 G2 (DI Water).

Figure 2. Comparison of 4-HPR in LXS™ matrix vs Capsule Formulation at 250 mg/kg/day. Cohorts of five mice were gavaged with 250 mg/kg/day of 4-HPR in LXS formulation LYM-X 5.60 in Slim-Fast® or in water, or 4-HPR expressed from capsules and mixed in Slim-Fast®, divided BID, x 4.5 days. Animals were sacrificed 3 hrs after the last dose and 4-HPR levels in plasma and tissues were assayed by HPLC. Results showed that LXS formulations, especially in Slim-Fast®, obtained significantly higher levels than the 4-HPR capsule formulation, except in brain tissue. PLASMA: G1 vs capsule, $P=0.006$; G2 vs capsule, $P=.008$; LIVER: G1 vs capsule, $P=.001$; G2 vs capsule, $P=0.01$; LUNGS: G1 vs capsule, $P=0.05$; G2 vs capsule, $P=0.035$; KIDNEY: G1 vs capsule, $P=0.013$; G2 vs capsule, $P=0.22$; BRAIN: G1 vs capsule, $P=0.187$; G2 vs capsule, $P=0.11$. Statistical analysis by Student's t -test. PLEASE NOTE CHANGE OF SCALE. Columns, in each set of columns, in sequence from left to right, represent LYM-X 5.60 GI (SLIMFAST™), LYM-X 5.60 G2 (DI Water), and 4-HPR Capsule in SLIMFAST™

Figure 3. Comparison of 4-HPR in LXS™ matrix vs Capsule Formulation at 560 mg/kg/day. In a pilot experiment, single mice were gavaged with 560 mg/kg/day of 4-HPR formulated in various LXS compositions or 4-HPR expressed from 4-HPR

capsules, divided BID, x 4.5 days. Animals were sacrificed 3 hrs after the last dose and 4-HPR levels in plasma and tissues were assayed by HPLC. Results showed that all LXS formulations apparently obtained much higher levels than the capsule formulation in plasma and liver and lung tissues, and LYM-X 5.60 exceeded capsule levels in kidney tissue. 4-HPR levels achieved in brain tissue using compositions LYM-X 5.59 and LYM-X 5.60 were about double that obtained using the capsule formulation. Columns, in each set of columns, in sequence from left to right, represent LYM-X 5.57, LYM-X 5.58, LYM-X 5.60, LYM-X 5.59, and Capsule Lot #R-6124.

Detailed Description of the Preferred Embodiments

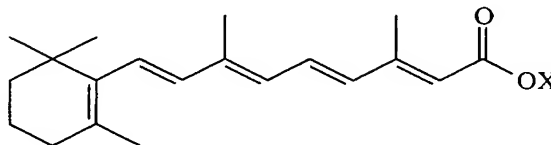
The present invention is explained in greater detail below. Applicants specifically intend that all United States patents cited herein be incorporated herein by reference in their entirety.

1. Active agents.

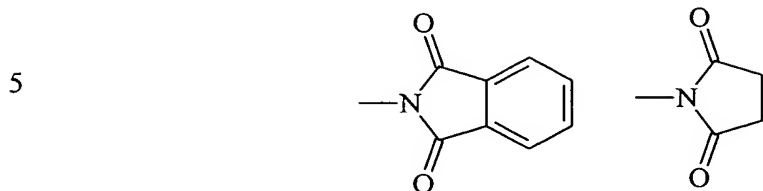
While the present invention is initially concerned with the delivery of retinides, a variety of different active agents can be used in carrying out the present invention. Examples of active agents that can be incorporated into the compositions and formulations of the present invention include, but are not limited to, paclitaxel, insulin, histrelin, β estradiol, nifedipin analogues, hydrochlorothiazide, McN-5703, capsaicin, diltiazem, renin inhibitors, hydrocortisone, cromolyn, pramoxine, buprenorphine, progesterone, cyclosporin A, metronidazole, and gentamicin. Retinides, particularly fenretinide, are currently preferred.

Retinides used for carrying out the present invention are, in general, ceramide-generating retinoids or retinoic acid derivatives. Such compounds include those described in U.S. Patent No. 4,190,594 to Gander (the disclosures of all patent references cited herein are incorporated herein by reference). Ceramide-generating retinoids include all trans-retinoic acid (ATRA) and retinoic acid derivatives, including but not limited to:

(A) esters of all-trans-retinoic acid having the following formula:

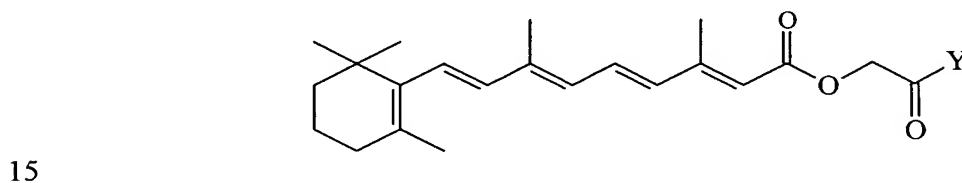


wherein X is a member selected from the group consisting of:



2-cyclohexylethyl; 10-carbomethoxydecyl; 4-hydroxybutyl; cholesteryl; mixed m- and p-vinylbenzyl; and 4-bromobenzyl;

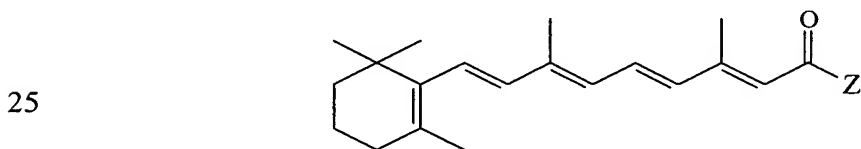
10 (B) esters of all-trans-retinoic acid having the following formula:



wherein Y is a member selected from the group consisting of: cholesteryloxy; phenyl; 4-bromophenyl; 4-methoxyphenyl; 4-nitrophenyl; 4-hydroxyphenyl; 4-methylphenyl; 4-cyanophenyl; 4-ethoxyphenyl; 4-acetoxyphenyl; 2-naphthyl; 4-biphenyl; 2,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2,4-dimethylphenyl; 3,4-diacetoxyphenyl; 3,4,5-trimethoxyphenyl; and 2,4,6-trimethylphenyl; and

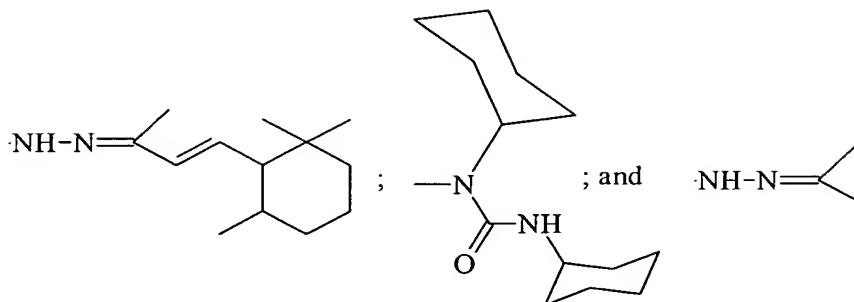
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(C) amides of all-trans-retinoic acid having the following formula:

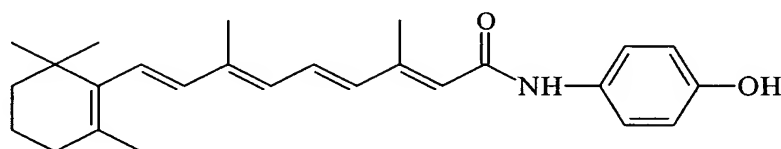


wherein Z is a member selected from the group consisting of: n-propylamino; tert-butylamino; 1,1,3,3-tetramethylbutylamino; 1-morpholino; 4-hydroxyphenylamino; 4-carbomethoxy-2-hydroxyphenylamino; beta-(3,4-dimethoxyphenyl)-ethylamino; 2-benzothiazolylamino; 1-imidazolyl; 1-(2-nicotinoylhydrazolyl); 1-benzotriazolyl; 1-(1,2,4-triazolyl);

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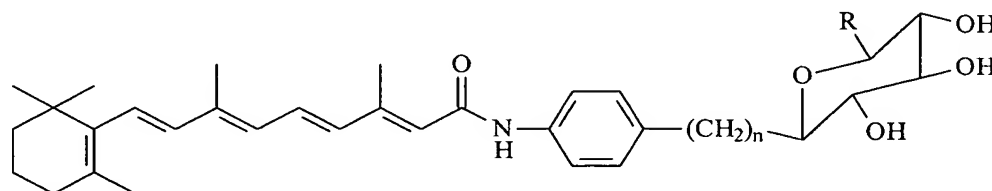


Particularly preferred is all-*trans*-N-(4-hydroxyphenyl)retinamide, also called fenretinide, which has CAS registry number 65646-68-6, and has the structure:



The foregoing compounds can be prepared in accordance with known techniques. *See, e.g.,* U.S. Patent No. 4,190,594 to Gander et al.; U.S. Patent No. 4,665,098 to Gibbs.

Additional retinoic acid derivatives that can be used to carry out the present invention include C-Glycoside analogs of N-(4-hydroxyphenyl)retinamide-O-glucuronide. Such compounds and their preparation are known and described in U.S. Patents Nos. 5,663,377 and 5,599,953, both to Curley et al., the disclosures of which are incorporated by reference herein in their entirety. Such compounds may have the general formula:



30 where R is COOH, CH₂OH, or H, and n is 0 or 1.

Specific examples of such compounds include: 4-(retinamido)phenyl-C-glucuronide; 4-(retinamido)phenyl-C-glucoside; 4-(retinamido)phenyl-C-xyloside; 4-(retinamido)benzyl-C-glucuronide; 4-(retinamido)benzyl-C-glucoside; 4-

(retinamido)benzyl-C-xyloside; 1-(β -D-glucopyranosyl) retinamide; and 1-(D-glucopyranosyluronosyl) retinamide.

2. Lipid matrix compositions.

5 Lipid matrix compositions that may be used to carry out the present invention generally comprise a combination of lysophosphatidylcholine, monoglyceride, and fatty acid. Without wishing to be bound to any particular theory of the invention, it is believed that the lipid matrix composition is non-liposomal (*e.g.*, in a lamellar phase, and non- or minimally-hexagonal phase and/or inverse hexagonal phase) and forms an
10 organized lipid matrix of lysophosphatidylcholine, monoglyceride and fatty acid that enfolds the active agent in acyl-constituents of the lipid matrix monomer backbones for absorption in the proximal intestine, with the monomers forming chylomicron-like elements that enter systemic circulation via the thoracic duct.

Lipid matrix compositions suitable for use in carrying out the present
15 invention are known and described in, for example, US Patent No. 4,874,795; US Patent No. 5,891,466; US Patent No. 5,972,911; US Patent No. 6,426,069; and PCT Application WO 03/031593, the disclosures of which applicant specifically intends be incorporated by reference herein in their entirety. In one embodiment useful for carrying out the present invention, the lipid matrix composition comprises:

- 20 (a) at least one non-esterified fatty acid having 14 to 18, or 14 to 22, carbon atoms (*e.g.*, palmitoleic, oleic, linoleic, or linolenic fatty acids);
- (b) at least one monoglyceride which is a monoester of glycerol and a fatty acid having 14 to 18, or 14 to 22, carbon atoms (*e.g.*, palmitoleic, oleic, linoleic, or linolenic fatty acids); and
- 25 (c) lysophosphatidylcholine in which the fatty acid moiety has 14 to 18, or 14 to 22, carbon atoms (*e.g.*, in which the fatty acid moiety is a palmitoleic, oleic, linoleic, or linolenic fatty acid).

In general, the fatty acids and monoglycerides together may comprise from about 70 mole percent to about 99 mole percent of the lipid matrix composition, the molar ratio
30 of the fatty acids to the monoglycerides may be from about 2:1 to about 1:2, and the lysophosphatidylcholine may comprises from about 1 mole percent to about 30 mole percent of the lipid matrix composition.

The lipid matrix compositions may be nonaqueous or minimally hydrated (e.g., containing less than 5, 6, 7 or 8, and preferably not more than 1, 2, 3 or 4, Moles of water per mole of lipid matrix composition). The lipid matrix composition may be in the form of colloidal particles. Where minimally aqueous the compositions may
5 further comprise (d) bicarbonate (e.g., wherein the concentration of the lysophosphatidylcholine is at least 0.1 mM in the minimally aqueous environment and the molar ratio of the bicarbonate to the lysophosphatidylcholine is greater than 1:1, greater than 1.4:1, or greater than 7:1), and optionally may further comprise (e) bile salts such as sodium taurocholate (e.g., wherein the molar ratio of the bile salts to the
10 lysophosphatidylcholine may be at least 10:1).

A particularly preferred composition for combination with the active agent is LYM-X-SORB™ drug matrix composition (see, e.g., G. Lepage, D. Yesair et al., *J. Pediatrics* **141**, 178-185 (2002)), available from BioMolecular Products, Inc., 136 Main Street, Byfield, MA 01922 USA (telephone 978-462-2244) or Avanti Polar
15 Lipids, Inc., 700 Industrial Park Drive, Alabaster, Alabama 35007 USA (telephone 205-663-24924; fax 205-663-0756) in a non-acidified and non-protonated and non-aqueous lipid matrix form (e.g., minimally hydrated) of predominantly lamellar phase and with minimal hexagonal or inverse hexagonal phase.

The active agent (e.g. a retinide such as fenretinide) may be readily combined
20 with the lipid matrix composition in any suitable amount, generally in a mole ratio of retinide:lipid matrix composition of from about 0.2:1 to about 2:1, more particularly about 0.4:1 to 1.5:1, and still more particularly about 0.6:1 to 1:1. The amount of active agent(s) in the composition may also be expressed as an amount by weight of the edible powder formulation, as further explained below.

25 While lipid matrix compositions as described above are preferred for carrying out the present invention, the invention can also be carried out with liposome compositions. Liposomes suitable for use in the composition of the present invention include those composed primarily of vesicle-forming lipids, as exemplified by the phospholipids. The liposomes can also include other lipids incorporated into the lipid
30 bilayers, with the hydrophobic moiety in contact with the interior, hydrophobic region of the bilayer membrane, and the head group moiety oriented toward the exterior, polar surface of the bilayer membrane. The vesicle-forming lipids are preferably ones having two hydrocarbon chains, typically acyl chains, and a head group, either

polar or nonpolar. There are a variety of synthetic vesicle-forming lipids and naturally-occurring vesicle-forming lipids, including the phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, phosphatidic acid, phosphatidylinositol, and sphingomyelin, where the two hydrocarbon chains are typically between about 14-22 carbon atoms in length, and have varying degrees of unsaturation. The above-described lipids and phospholipids whose acyl chains have varying degrees of saturation can be obtained commercially or prepared according to published methods. Other suitable lipids include glycolipids and sterols such as cholesterol. *see, e.g.*, US Patent No. 6,355,268; *see also* US Patent Nos. 6,673,364; 6,660,525; and 5,773,027 (the disclosures of which applicants specifically intend be incorporated herein by reference).

3. Edible powder formulations.

In a preferred embodiment of the invention, the mixture or complex of active agent (such as retinide) and lipid matrix composition is mixed with additional ingredients to form a free-flowing, edible powder of solid particulate matter (*e.g.*, as opposed to a liquid). Such additional ingredients include sweeteners, flours, humectants, etc. In general, such a composition may comprise or consist essentially of:

(a) from about 1 or 2 up to about 4, 6 or 10 percent by weight of active agent (such as retinide);

(b) from about 5 or 10 up to about 30 or 40 percent by weight of lipid matrix composition as described above;

(c) optionally, but in some embodiments preferably, from about 1, 2, 5 or 10 up to about 30 or 40 percent by weight of sweetener (lower amounts being possible by inclusion of high intensity sweeteners as discussed below);

(d) from about 20, 30 or 40 up to about 60, 70 or 80 percent by weight flour; and

(e) optionally, from 0 or 1 up to about 10, 16 or 20 percent by weight of a humectant (as needed or desired depending upon choice of sweetener and other ingredients).

Additional optional ingredients may include small amounts of salt, colorants, preservatives, stabilizers, antimicrobials, anti-caking additives, etc., as is conventional in the art.

Sweeteners that may be used in preparing formulations of the invention include, but are not limited to, sugars such as sucrose, dextrose, fructose, maltodextrin, glucose, tagatose, lactose, invert sugar, maltose, etc., as well as high intensity sweeteners such as sucralose, sodium cyclamate, sodium saccharin, aspartame, etc. All such sweeteners may be used alone or in combination with one another.

Any edible fine dry powder produced by grinding a nut, cereal grain or other source of plant starch or carbohydrate may be used as the flour in the present invention. Suitable flours include but are not limited to rice flour, potato flour, corn flour, masa corn flour, tapioca flour, buckwheat flour, wheat flour, oat flour, bean flour, barley flour rye flour, millet flour, sorghum flour, chestnut flour, and mixtures thereof. The flour may optionally have additional ingredients such as preservatives and flowing agents included therein.

Humectants may optionally be included in the composition where necessary or desired to, among other things, lower the a_w of the composition. Examples of humectants include, but are not limited to, corn syrup, high fructose corn syrup, polyhydric alcohols (e.g., sorbitol, glycerol, xylitol and the like), polydextrose, combinations thereof, etc. In some embodiments, the compositions have an water activity (or " a_w ") less than 0.85 (to reduce pathogen growth therein); in some embodiments the compositions have an a_w less than 0.65 (to reduce growth of osmotolerant yeasts and molds therein).

Flavorants that may optionally be included in the composition include, but are not limited to: almond nut, amaraetto, anisette, banana, tapioca, brandy, cappuccino, mint, cinnamon, cinnamon almond, creme de menthe, orange, peppermint stick, pistachio, licorise, apple, chamomile, cinnamon spice, creme, vanilla, french vanilla, lemon, macadamia nut, orange, orange leaf, peach, strawberry, grape, raspberry, cherry, coffee, chocolate and the like, aroma enhancers such as acetaldehyde, herbs, spices, mocha, butternut, rum, hazelnut, horchata, dulce de leche, etc., as well as mixtures of these flavors. *See, e.g.*, US Patent No. 6,207,206.

Compositions of the invention can be made by, first, combining an active agent (such as a retinide) with a lipid matrix composition as described above. The lipid matrix composition is preferably non-acidic or basic, and preferably contains less than 7 or 8 moles of water (and more preferably not more than 3 moles of water) per mole of lipid matrix. The combining step may be carried out by heating the lipid matrix composition to form a soft or viscous or oily composition and then stirring or mixing the active agent therein to form a soft or viscous or oily product. The viscous/oily product is then mixed with flour and optionally sweetener (and other optional ingredients as desired), with the mixing being carried out with sufficient shear stress (*e.g.*, by stirring or blowing) to produce a flowable powder composition as described herein. For example, mixing can be carried out by pouring the flour (and optionally sweetener) into the viscous/oily product with concurrent stirring in a food processor, blender, commercial mixer or blender, or the like. The speed of the mixing apparatus can be varied as desired throughout the process: *e.g.*, with mixing being carried out at a lower speed to initially combine the ingredients, and then the speed increased as desired to produce the flowable powder composition described herein.

The flowable powder may be packaged in bulk or unit dose containers such as packets or sealed cups for subsequent use, with unit dose containers preferably containing from 1 to 10 or 20 grams of the flowable powder.

The flowable powder may be consumed or administered *per se* to a subject. The flowable powder may, if desired, be caked or baked into a formed food product such as a cookie, wafer, or bar for subsequent consumption by a subject. The flowable powder may, if desired, be mixed with another liquid, solid, or semi-solid food or nutritional supplement for administration to a patient (examples including but not limited to oatmeal or other grain meals, pudding, ice creams, sorbet, apple sauce, liquid soy-based nutritional supplement compositions such as SLIM-FAST™ and fruit juice). Preferably the foods or compositions with which the powder is mixed do not contain lipid-matrix destabilizing agents such as milk fat (*e.g.*, replacing milk fats with soy fats).

4. Treatment and Administration.

The present compositions and formulations can be administered for the treatment of hyperproliferative disorders such as tumors, cancers, and neoplastic

disorders, as well as premalignant and non-neoplastic or non-malignant hyperproliferative disorders, or for the treatment of other medical conditions in need of treatment, such as hypertension, infection, inflammation, graft versus host disease, etc.

5 Subjects to be treated by the compositions, formulations and methods described herein are, in general, mammalian subjects, including both human subjects and animal subjects such as dogs, cats, horses, etc. for veterinary purposes. The subjects are, in some embodiments, infant, juvenile, or geriatric subjects.

10 Examples of tumors, cancers, and neoplastic tissue that can be treated by the present invention include but are not limited to malignant disorders such as breast cancers; osteosarcomas; angiosarcomas; fibrosarcomas and other sarcomas; leukemias; lymphomas; sinus tumors; ovarian, ureteral, bladder, prostate and other genitourinary cancers; colon, esophageal and stomach cancers and other gastrointestinal cancers; lung cancers; myelomas; pancreatic cancers; liver cancers;
15 kidney cancers; endocrine cancers; skin cancers; and brain or central and peripheral nervous (CNS) system tumors, malignant or benign, including gliomas and neuroblastomas.

 Examples of premalignant and non-neoplastic or non-malignant hyperproliferative disorders include but are not limited to myelodysplastic disorders;
20 cervical carcinoma-in-situ; familial intestinal polyposes such as Gardner syndrome; oral leukoplakias; histiocytoses; keloids; hemangiomas; hyperproliferative arterial stenosis, inflammatory arthritis; hyperkeratoses and papulosquamous eruptions including arthritis. Also included are viral induced hyperproliferative diseases such as warts and EBV induced disease (*i.e.*, infectious mononucleosis), scar formation, and
25 the like. The methods of treatment disclosed herein may be employed with any subject known or suspected of carrying or at risk of developing a hyperproliferative disorder as defined herein.

 As used herein, "treatment" of a hyperproliferative disorder refers to methods of killing, inhibiting or slowing the growth or increase in size of a body or population
30 of hyperproliferative cells or tumor or cancerous growth, reducing hyperproliferative cell numbers, or preventing spread to other anatomic sites, as well as reducing the size of a hyperproliferative growth or numbers of hyperproliferative cells. As used herein, "treatment" is not necessarily meant to imply cure or complete abolition of

hyperproliferative growths. As used herein, a treatment effective amount is an amount effective to result in the killing, the slowing of the rate of growth of hyperproliferative cells, the decrease in size of a body of hyperproliferative cells, and/or the reduction in number of hyperproliferative cells.

5 The therapeutically effective dosage of any one active agent, the use of which is in the scope of present invention, will vary somewhat from compound to compound, patient to patient, and will depend upon factors such as the condition of the patient and the route of delivery. Such dosages can be determined in accordance with routine pharmacological procedures known to those skilled in the art, particularly
10 in light of the disclosure provided herein. For fenretinide, a dose to achieve a plasma level of about 1 μ M to 10 or 50 μ M, or greater, is employed (*e.g.*, an oral dose of 10 or 20 to 500 or 1000 mg of fenretinide).

Feeding of the compositions of the invention may be carried out by any of a variety of procedures. The subject may be fed the composition orally and directly.
15 The composition may be diluted or combined in a food or beverage prior to feeding to a subject.

The feeding may be carried out by feeding the subject through a gastric, jejunal, naso-gastric or nasal-jejunal feeding tube, in which case feeding preferably involves (*i*) combining the dry powder with a preferably non-lipid matrix
20 destabilizing liquid (*e.g.*, one substantially free of milk fat) to produce a liquid composition, and then (*ii*) delivering the liquid composition to the subject through the feeding tube.

Particularly suitable subjects for administering or feeding the compositions described herein are infant, juvenile or geriatric subjects.

25 The compositions described herein may be used in combination therapies, such as described in B. Maurer et al., US Patent No. 6,368,831, or B. Maurer et al., U.S. Patent No. 6,352,844, the disclosures of which are incorporated by reference herein in their entirety.

The present invention is explained further in the non-limiting Examples set
30 forth below.

EXAMPLE 1

Oral Compositions of 4-HPR

The actual dose of 4-HPR to be delivered to patients will ultimately define the resulting mixture volume, once it is determined. These arbitrary values present 4-HPR doses of 0.5 to 2.5 grams per mixture volume.

A concentrated LXS-HPR mixture would be >1000 mg HPR per 10 cc. As awkward as this may be for typical dosage calculations, we usually describe [drug]-LXS ratios in terms of moles. This is because our prior work suggests that 1 mole of drug successfully interacts within the inclusion space of 1 mole of LXS. So, if we use a mole ratio of 0.8 (0.8 moles of drug per mole of LXS), the maximum concentrated dosage would be $397 \times 0.8 / 2429$, or 131 mg HPR per gram of LXS.

In reading **Table 1**, then, with a mole ratio of 0.8, 2.5 g of 4-HPR would complex with 19.09 g LXS with a resulting total volume of 17.18 ml, or approximately 1400 mg per 10 cc. The calculations for lower mole ratios are included.

Preferably, the LXS composition (in the form of an oil) is mixed with 4-HPR first. Once dissolved in the oil, a small initial amount of basic water (such as containing the bicarbonate of soda) is mixed in to the composition to soften the composition to a foam. The resulting foam may then be mixed with a suspension agent (*e.g.*, SLIMFAST™ soy beverage or more water) via probe sonication. Alternatively, the composition containing 4-HPR or other medicinal agent in the LXS can be compounded directly with edible food compositions or excipients.

Table 1: 4-HPR:LXS Mixture Concentrations

4-HPR:LXS Mole Ratio	wt 4-HPR (g)	wt Corresponding LXS (g)	Mixture Volume (cc)
0.60	0.50	5.09	4.58
	1.00	10.18	9.16
	1.50	15.27	13.75
	2.00	20.36	18.33
	2.50	25.45	22.91
0.65	0.50	4.70	4.23
	1.00	9.40	8.46
	1.50	14.10	12.69
	2.00	18.80	16.92
	2.50	23.50	21.15
0.70	0.50	4.36	3.93
	1.00	8.73	7.85
	1.50	13.09	11.78
	2.00	17.45	15.71
	2.50	21.82	19.64
0.75	0.50	4.07	3.67
	1.00	8.15	7.33
	1.50	12.22	11.00
	2.00	16.29	14.66
	2.50	20.36	18.33
0.80	0.50	3.82	3.44
	1.00	7.64	6.87
	1.50	11.45	10.31
	2.00	15.27	13.75
	2.50	19.09	17.18

EXAMPLE 2

Improved Bioavailability of oral 4-HPR using LYM-X-SORB™ Lipid Matrix

5 LYM-X-SORB™ (Lymphatic Xenobiotic Absorbability) lipid matrix (also referred to as LXS™ herein) is a patented and proprietary technology of LYM-DRUG PRODUCTS, LLC and BioMolecular Products, Inc., Byfield, MA, useful for increasing the oral bioavailability of water insoluble compounds. LXS™ is a non-liposomal, lipid-based, drug delivery system composed of FDA-accepted GRAS (Generally Regarded
10 As Safe) lipids (lysophosphatidylcholine (LPC), monoglycerides (MG), and fatty acids (FA)). LXS™ acts as a "lipid-fingered glove" which wraps around the drug of interest in a 1:1 molar ratio. In the presence of sodium bicarbonate and bile salts, the LXS/drug matrix forms < 10 nm size particles that are readily absorbed. Neither the LXS™ monomer, nor the LXS/drug matrix, damage intestinal villae. LXS™ has been
15 demonstrated safe in a one-year double blind oral feeding trial in Cystic Fibrosis (CF) children (Lepage, et al. J Pediatr. 114:178-185, 2002.) Diverse, minimally-soluble, drugs have been shown to be compatible with LXS™, including 4-HPR (U.S. Patent No. 4,874,795). In beagle dogs, LXS™ increased the peak plasma concentration of 200 mg doses of 4-HPR by 5-fold, and increased mean area under the curve (AUC) by 4.2-
20 fold compared to the current oral capsular formulation (of Gibbs)(U.S. Patent No. 4,665,098) (). In single-dose experiments in healthy human volunteers, plasma concentrations equivalent to those obtained using the current capsular 4-HPR formulation were achieved using 1/5 the 4-HPR dose in a LXS™ formulation. These results suggested that a liquid formulation of 4-HPR with increased bioavailability
25 might be possible using LXS™ technology.

To test this hypothesis, we had various LXS™ compositions of 4-HPR prepared that varied in the LPC:MG:FA ratios of the LXS™ matrix. We then feed mice with equal doses of 4-HPR in the LXS™ compositions, or expressed as a slurry from the current oral 4-HPR capsules. Steady state plasma and tissue levels of 4-HPR were
30 assayed after animal sacrifice. The results demonstrated that 4-HPR plasma and tissue levels were dose-dependent, and that certain LXS™ formulations obtained significantly higher steady-state 4-HPR plasma and tissues than those achieved by the current

capsular formulation, especially at higher doses (**Figures 1, 2, and 3**). All animals completed the experiments. No obvious toxicities were observed. In Figure 1:

LYM-X 5.57 = 1:2:4 lysophosphatidylcholine:monoglycerides:fatty acid (LPC:MG:FA);

5 LYM-X 5.58 = 1:4:2;

LYM-X 5.59 = 1:4:2 with some base (bicarb) added during processing in an amount sufficient to soften the oily mixture to a foam as discussed above;

LYM-X 5.60 = 1:3:3; and

10 G1, G2 = LYM-X 5.60 in water or SLIMFAST™ soy beverage

The LYM-X-5.59 composition is currently preferred.

EXAMPLE 3

Powder Formulation Process.

15 A 1:0.8 Mole ratio combination of LYM-X-SORB™ drug matrix composition was combined with fenretinide in accordance with known techniques and as described in Example 1 above in a 1:0.8 Mole ratio to form an LXS/4-HPR complex. The lipid matrix is not acidified or significantly hydrated to form a protonated aqueous lipid matrix of predominantly hexagonal or inverse hexagonal
20 phase. Rather, the lipid matrix is basic, minimally-hydrated, and of predominantly lamellar phase. The LXS/4-HPR is blended to an oil and stored at -20°C. The oil is ~88.8% (wt) LXS and 11.2% (wt) 4-HPR (1:0.8 mole ratio).

A food processor is used for the blending to a powder but this may be replaced by a much larger reactor vessel with internal chopper blades or other mixing device to
25 process multiple kilos simultaneously. Either way, the flour and sugar are loaded into the blending vessel and mixed for ~1 minute or more at room temperature. The LXS/4-HPR is then loaded at ambient temperature as a semi-solid to the flour/sugar. Allowing the LXS/4-HPR to warm to room temperature for ~1 hour prior to loading provides a thick material capable of scooping in solid pieces similar to butter. The
30 combination is then mixed at room temperature via the blending device (on high) for ~2-3 minutes or until no solid LXS/4-HPR is noted. The resulting powder is bright yellow and free flowing with mild agglomerations that are easily broken apart upon

examination. This material is discharged and weighed into the respective containers.
Constituent ranges are:

- 53.5% (wt) wheat flour,
- 19.6% (wt) granulated sugar,
- 5 23.8% (wt) LXS and
- 3.1% (wt) 4-HPR.

These weights, to date, have not had much discrepancy so the ranges are relatively tight ($\pm 1\%$) but in some preferred embodiments the final product may comprise at least 22-27% total lipid and 2.5-3.5% 4-HPR.

- 10 Salt and bicarbonate may be added in limited amounts (preferably not more than about 1%). Corn syrup may be added up to 15%, but in combination with 15% LXS the mixture becomes too thick for powder work.

- The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with
- 15 equivalents of the claims to be included therein.